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INTERVET INC
405 STATE STREET
PO BOX 318
MILLSBORO, DE 19966

EXAMINER

BASKAR, PADMAVATHI

ART UNIT

PAPER NUMBER

1645

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/034,500

Applicant(s)

JACOBS ET AL.

Examiner

Padmavathi v Baskar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9, 13, 18-21 and 38 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 9, 13, 18-21 and 38 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

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Response to Amendment

1. Applicant's amendment filed on 10/29/03 and 11/14/03/ is acknowledged. Claims 1-8, 10-12, 14-17 and 22-37 are cancelled. Claims 9, 13, 18- 21and 38 have been amended. Claims 9, 13, 18- 21 and 38 are pending in the application and are under prosecution.
2. Applicant's amendment to the specification and submission of additional primer sequences in response to the Office action is acknowledged.

Claim objections and Rejections Withdrawn

3. In view of amendment to the claim 38, the objection under 37 CFR 1.75(c) as being in improper multiple dependent form is withdrawn.
4. In view of amendment to the claims the rejection under 35 U.S.C. 101 is withdrawn.
5. In view of amendment to the claims, the rejections under 35 U.S.C. 112, first paragraph written description and enablement are withdrawn.

New Claim Rejections based on amendment

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 9, 13, 18-21 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at

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Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to an isolated *Lawsonia intracellularis* outer membrane protein and immunogenic composition comprising an amino acid sequence homologous to SEQ.ID.NO: 2 being immunoreactive with antisera to SEQ ID NO: 2 and having molecular weight about 37KD, said Outer Membrane Protein being obtainable by a process comprising the steps of

- a) subjecting an outer membrane preparation to SDS-PAGE and
- b) excision of the 37 KD band from the gel, and an immunogenic fragment of said protein. (The examiner is considering fragments and an amino acid sequence homologous to SEQ.ID.NO: 2 as variants and hereafter will be referred to variants).

The specification broadly describes as part of the invention, an isolated protein of SEQ ID NO: 2, which is a " 37kD outer membrane protein "on page 2, lines 19 and 20. The specification also teaches on page 22 that 37 kD protein has been amplified and cloned as a 656 bp product. However, the specification does not teach fragments of *Lawsonia intracellularis* protein.

The actual biological function of the protein represented as SEQ ID NO: 2 is not set forth in this specification. Applicants broadly describe fragments of *L.intracellularis* protein of the invention as embracing any deletion by use of language in which specified amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The specification does not teach an isolated homologous *Lawsonia intracellularis* outer membrane protein or immunogenic composition comprising homologous to SEQ.ID.NO: 2 being immunoreactive with antisera to SEQ ID NO: 2. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See

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page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, an isolated *Lawsonia intracellularis* outer membrane protein and immunogenic composition comprising the amino acid sequence SEQ.ID.NO: 2, being immunoreactive with antisera to SEQ ID NO: 2 and having molecular weight about 37KD, said outer membrane protein being obtainable by a process comprising the steps of

a) subjecting an outer membrane preparation to SDS-PAGE and

b) excision of the 37 KD band from the gel meet the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach a protein homologous to SEQ ID NO: 2 that reacts with antisera to SEQ.ID.NO: 2 and it is noted that the claimed variants do not exist as an invention independent of their function in encoding a protein. The actual structure or other relevant identifying characteristics of each protein (i.e. homologous) having the claimed properties of the 37 kD protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability and testing each to determine whether such a protein ^{has} ~~having~~ the particularly disclosed properties of an 37 kD protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function. This specification does not teach such, and the art is devoid of this correlation for SEQ ID NO: 2, 37kD protein with undetermined function. There is no written description support for homologous protein or fragments of SEQ ID NO: 2 as claimed.

The 37kD protein comprising SEQ ID NO: 2 is uncharacterized by this specification and is not asserted to belong to any known family of proteins. The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ.ID.NO: 2

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(37 kD protein) variants/fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 U5PQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc V Chugai Pharmaceutical Co Ltd.*, 18 U5PQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 U5PQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

8. Claims 9, 13, 18-21 and 38 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated *Lawsonia intracellularis* outer membrane protein and immunogenic composition comprising the amino acid SEQ.ID.NO: 2, being immunoreactive with antisera to SEQ ID NO: 2 and having molecular weight 37KD, said Outer Membrane Protein being obtainable by a process comprising the steps of

a) subjecting an outer membrane preparation to SDS-PAGE and

b) excision of the 37 KD band from the gel, the specification does not reasonably provide enablement for an amino acid sequence homologous to SEQ.ID.NO: 2 or fragments of 37KD protein or fragments of SEQ, ID.NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims since there is no written description support for the claimed invention.

These claims are not enabled for the following reasons. The written description is limited to only SEQ ID NO: 2 which is a 37kD protein comprising the amino acid sequence SEQ ID NO: 2 and described as an outer membrane protein of *L. intracellularis*. The specification fails to indicate homologous *Lawsonia* protein and fragments of SEQ ID NO: 2 and fails to teach that

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the claimed antigenic fragments are detected by immune sera and further lacks any description of any such fragments. The specification is not enabled for any variant /fragment of a protein comprising SEQ ID NO: 2 because 1) the specification fails to teach protein that is homologous with SEQ ID NO: 2 or fragment thereof is able to function by binding immune sera; 2) the specification fails to teach how to make and use variants/fragments thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical protein residues that can be modified and still achieve a protein with functional activity 4) the art teaches that proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of such antigen variants or antigenic fragments of SEQ ID NO:2, and 5) applicants have not displayed a nexus between the structure and function of the claimed fragments/variants. As to points 1)- 5), the specification fails to provide a written description of any protein variants/fragments of a bacterial protein sequence of SEQ ID NO: 2. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO: 2 as such the skilled artisan is provided no guidance to test, screen or make variants/fragments of the protein comprising SEQ ID NO: 2. The specification fails to teach to what extent one could alter SEQ ID NO: 2 and still present the sequence as a functional protein. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position

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118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol, 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a protein that is functional. Since, the specification lacks a written description of any variants of SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed variants or fragments of SEQ.ID.NO: 2 as well as how to use the claimed fragments of SEQ ID NO: 2. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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10. Claims 9, 13, 18-21 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is vague in reciting " 37 KD band from the gel and an immunogenic fragment of said protein" It is not clear to what immunogenic fragments applicant is referring?

Claim 13 is rejected as being vague for the recitation of " homologous?" It is not clear what homologous protein the claim is referring to, as claim 13 appears to be further limiting claim 9?

Claim 19 recites, "characterized in that". It is not clear what does applicant intend to mean by "characterized in that"? Does applicant intend the claim to mean " the immunogenic composition according to claim 18 further comprises an adjuvant"?

Claim 20 recites the limitation "antigen" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites, "characterized in that". It is not clear what does applicant intend to mean by "characterized in that"? Does applicant intend to mean " the immunogenic composition according to claim 18 further comprises an additional protein"?

Claim 21 recites "characterized in that". It is not clear what does applicant intend to mean by "characterized in that"?

Claim 21 is objected to because of the following informalities: claim recites an improper Markush group language. Appropriate correction is required.

Claims 18 and 38 are rejected as being vague and not clear for the recitation of " a protein". It is not clear what protein is being claimed, the protein of claim 9 or something else?

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Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 9, 13, 18-21 and 38 * rejected under 35 U.S.C. 102(b) as being anticipated by McOrist, S., Boid, R. and Lawson, G. H. K. 1989. Infect. Immun. 57: 957- 962.

The claims are drawn to an isolated *Lawsonia intracellularis* outer membrane protein and immunogenic composition comprising an amino acid sequence homologous to SEQ.ID.NO: 2 being immunoreactive with antisera to SEQ ID NO: 2 and having molecular weight about 37KD, said Outer Membrane Protein being obtainable by a process comprising the steps of

a) subjecting an outer membrane preparation to SDS-PAGE and

b) excision of the 37 KD band from the gel, and an immunogenic fragment of said protein.

McOrist et al disclose Campylobacter-like organism (later designated as *L. intracellularis* bacteria) isolated from homogenized intestinal tissue of three pigs and bacteria was cultivated, intracellular bacteria was extracted, whole cell suspension was used to prepare immunogen for raising monoclonal antibodies (page 957-958 under Materials and Methods). Sonicated outer membrane antigens were separated by SDS-PAGE analysis and immunoblotted using monoclonal antibodies. Outer membrane proteins ranging from 25KD- 43 KD were identified (figure 2) as specific for Campylobacter-like organism, also now known as *L. intracellularis*. Thus the prior art disclosed outer membrane proteins read on the claimed invention because

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the outer membrane proteins ranging from 25KD- 43 KD contain 37KD protein. Applicant's use of the open-ended term "comprising " in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Therefore, the claims read on the isolated outer membrane protein which inherently comprises the amino acid sequence as set forth in the SEQ.ID.NO: 2 including immunogenic fragments of said protein. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). In the absence of evidence to the contrary the disclosed prior art outer membrane proteins and the claimed protein are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated protein with the proteins of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

13. Claims 9, 13, 18-21 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al Infection and Immunity, December 2000, p. 6737-6743, Vol. 68, No. 12.

Claims are discussed supra

Smith et al disclose bacteria were isolated from homogenized intestinal tissue and grown in cell culture in IEC-18 intestinal epithelial cells. Following isolation and serial passage in the laboratory for up to nine passages, this strain can reproduce disease in experimentally inoculated pigs. From pure, frozen stocks of bacteria, *L. intracellularis* was cultured to a final number of 11 passages; cells were then lysed and bacterial suspensions were prepared in SPG (sucrose-potassium-glutamate) buffer with 5% fetal calf serum (Page 6738 under Bacteria and preparation of inoculum in Materials and methods section). The cell lysate obtained from isolating bacterial preparation read on the claimed invention as the cell lysate comprises membrane proteins including immunogenic fragments of *Lawsonia intracellularis* outer

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membrane protein. Applicant's use of the open-ended term "comprising " in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Therefore, the claims read on cell lysate obtained from isolating bacterial preparation which inherently comprises the amino acid sequence as set forth in the SEQ.ID.NO: 2 including immunogenic fragments of said protein as the cell lysate used to raise antibodies in animals. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). In the absence of evidence to the contrary the disclosed prior art cell lysate and the claimed protein are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated protein with the lysate comprising protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

14. No claims are allowed.

Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire **THREE MONTHS** from the date of this action. In the event a first response is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (571) 272-0853. The examiner can normally be reached on Monday through Friday from 6:30 A.M. to 4:00 P.M. EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Padma Baskar Ph.D.

2/5/04

L. F. S.
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600